Limiting Excessive Postoperative Blood Transfusion after Cardiac Procedures

A Review

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Analysis of blood product use after cardiac operations reveals that a few patients (≤20%) consume the majority of blood products (>80%). The risk factors that predispose a minority of patients to excessive blood use include patient-related factors, transfusion practices, drug-related causes, and procedure-related factors. Multivariate studies suggest that patient age and red blood cell volume are independent patient-related variables that predict excessive blood product transfusion after cardiac procedures. Other factors include preoperative aspirin ingestion, type of operation, over- or underutilization of heparin during cardiopulmonary bypass, failure to correct hypothermia after cardiopulmonary bypass, and physician overtransfusion.

A survey of the currently available blood conservation techniques reveals 5 that stand out as reliable methods: 1) high-dose aprotinin therapy, 2) preoperative erythropoietin therapy when time permits adequate dosage before operation, 3) hemodilution by harvest of whole blood immediately before cardiopulmonary bypass, 4) autologous predonation of blood, and 5) salvage of oxygenator blood after cardiopulmonary bypass. Other methods, such as the use of ε-aminocaproic acid or desmopressin, cell saving devices, reinfusion of shed mediastinal blood, and hemofiltration have been reported to be less reliable and may even be harmful in some high-risk patients.

Consideration of the available data allows formulation of a 4-pronged plan for limiting excessive blood transfusion after surgery: 1) recognize the causes of excessive transfusion, including the importance of red blood cell volume, type of procedure being performed, preoperative aspirin ingestion, etc.; 2) establish a quality management program, including a survey of transfusion practices that emphasizes physician education and availability of real-time laboratory testing to guide transfusion therapy; 3) adopt a multimodal approach using institution-proven techniques; and 4) continually reassess blood product use and analyze the cost–benefits of blood conservation interventions. ***(Tex Heart Inst J 1995;22:216-30)***

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Homologous blood transfusion during and after cardiac operations is associated with greater postoperative morbidity (including more disease transmission[1,2] and greater risk of infection and immunosuppression[3,4]) and higher procedural costs.[5,6] Coronary artery bypass grafting (CABG) and other cardiac procedures are among the most frequently performed operations and account for approximately 10% of all red blood cell units transfused.[7] Competing forces have kept the use of blood products from decreasing. For example, patients undergoing cardiac procedures are older and at higher risk, and often require longer operations and greater use of blood products. At the same time, efforts have been undertaken to reduce patient exposure to homologous blood through aggressive blood conservation strategies.[8-11] The action of these 2 forces generally results in a spectrum of blood product transfusion similar to that shown in Figure 1, which introduces data from patients undergoing CABG at our institution in 1993. This distribution pattern has been duplicated at other institutions[12] (by VAF) and is a surprisingly consistent reflection of transfusion incidence for CABG in particular, and for cardiac procedures in general. One remarkable feature of this distribution is that approximately 20% of patients account for more than 80% of the total blood product transfusion required in patients undergoing cardiac procedures. For the purposes of this review, and based on results similar to those shown in Figure 1,

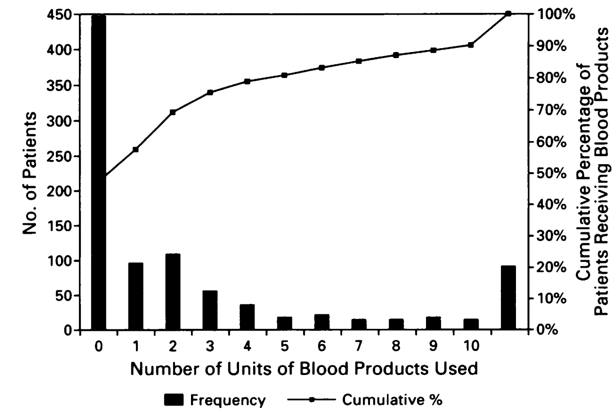

Fig. 1 *Distribution frequency of blood product transfusion in 939 patients undergoing coronary artery bypass grafting at Albany Medical Center in 1993.*

we consider patients who have received more than 4 units of homologous donor blood products as having been exposed to excessive blood product transfusion after cardiac surgery. This means that about 20% of patients undergoing CABG procedures are in a high-risk category, and these patients consume more than 80% of the blood products transfused.

Analysis of excessive blood product use in cardiac surgical patients suggests that patient factors, transfusion practices (physician-related), drug usage (aspirin and heparin), and procedure-related factors contribute to the disproportionate amount of blood products used in certain patients.[11-19] This review seeks to identify the causes of excessive transfusion and to examine blood conservation measures that are taken in order to limit excessive postoperative blood product use. Synthesis of such information allows formulation of a therapeutic strategy to limit excessive use of postoperative blood products.

Causes of Excessive Blood Transfusion

Patient-Related Causes

The frequency distribution of blood transfusion, as seen at our institution (Fig. 1), suggests that the greatest gains in limiting postoperative blood product transfusion will be made by focusing on the subset of patients in whom the most blood products are used. Variables that place patients at high risk for excessive blood product transfusion have not been well described, but analysis of the current literature allows some conclusions to be drawn.

Perhaps the most important preoperative variable associated with excessive blood product use is the packed red blood cell volume (blood volume times hematocrit), which is a combination variable that accounts for both preoperative anemia and low circulating blood volume and, in addition, has intuitive appeal. For example, older women (with lower circulating blood volume than that of age- and size-matched males) may have preoperative anemia from any of several causes (including iatrogenic causes such as recent cardiac catheterization or frequent drawing of blood while in the coronary care unit). Such patients are likely to require excessive postoperative blood product transfusion simply to offset normal operative blood loss and the loss that occurs as a result of hemodilution. The red blood cell volume (RBCVOL) is a variable that quantitates this clinical impression, and its components have been found to be independent predictors of excessive blood product transfusion in several studies.[11,12,16]

The RBCVOL also correlates with postoperative hospital length-of-stay, as shown by our results in Figure 2. It would seem that patients who require excessive blood transfusion would tend to be hospitalized longer after operation, but we* and others have not been able to identify such an association.[20] In fact, 1 study suggests that patients whose blood volume is replaced to the extent that their discharge hematocrit level is greater than 33% have a significantly shorter length-of-stay in the hospital compared with patients who have lower discharge hematocrit levels.[20] Two divergent factors may account for this lack of correlation. One is that there is a tendency for some physicians to over-transfuse patients, which may result in excessive blood product transfusion unrelated to serious illness. The 2nd is that some patients require excessive blood product transfusion because of a genuine hemorrhagic diathesis after operation. The causes of the diathesis can be multiple, but this complication is different from simple over-transfusion. In the case of simple over-transfusion, no prolongation in hospital stay is expected, while in the case of hemorrhagic diathesis,

*Ferraris VA. Unpublished observation, 1993.

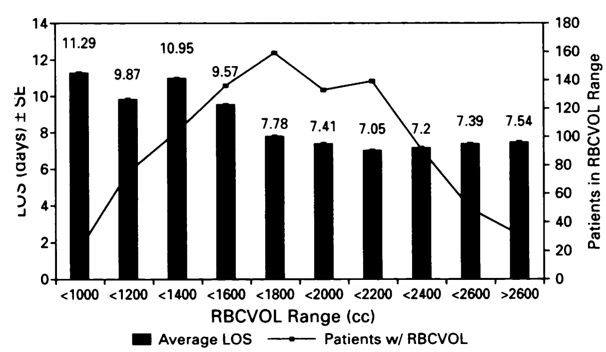

Fig. 2 *Effect of preoperative red blood cell volume on hospital length-of-stay in 939 coronary artery bypass grafting patients at Albany Medical Center during 1993.*

LOS = length-of-stay; RBCVOL = red blood cell volume; SE = standard error of the mean prolonged hospitalization might well occur. Because these 2 competing forces, and probably others, contribute to excessive blood product use after operation, the lack of association between hospital length-of-stay and excessive blood product transfusion is not surprising.

Advanced patient age has been shown to be a risk factor for blood product transfusion after CABG. Older age correlates with decreased bone marrow reserves and may be useful as an index of decreased circulating blood volume, much like RBCVOL.[12] Older patients (>70 years) have an above-average incidence of significant postoperative mediastinal hemorrhage, and this risk of bleeding seems to correlate with higher postoperative mortality rates.[19]

Physician-Related Causes ("Transfusion Triggers")

Controversy exists regarding the optimal hemoglobin level for patients during the period immediately after cardiopulmonary bypass (CPB). Most patients subjected to self-limiting anemia can tolerate hemoglobin levels as low as 7 g/dL, although tolerance of this level of anemia has been questioned in older literature.[21] More recent literature suggests that self-limited hemodilution to a hematocrit level of 15% may be tolerated in anesthetized human beings after coronary artery bypass surgery without serious sequelae.[22] For patients who have impaired cardiovascular status or chronic anemia, there are insufficient data to determine the lower limits of postoperative anemia or coagulation abnormalities that can be tolerated; therefore, transfusion practices are especially susceptible to clinical judgment. Although clinical guidelines for blood product transfusion have been developed[23-28] (Table I), there is still wide variability in the amount of blood products transfused in similar groups of patients by different physicians.[6,15,18,29,30] Some improvement in this inexact process has been reported with the use of transfusion algorithms based on standard guidelines,[31] but much work remains to be done in this area.

The most important factor in reducing excessive postoperative blood transfusion may be the education of physicians in transfusion practices and the use of standardized transfusion algorithms. A necessary preliminary step is a review of the blood transfusion practices in use at a particular institution, because of the variability in attitudes and practices with regard to postcardiac surgical blood transfusion.[15] Improving the process of blood transfusion practices is analogous to initiating total quality management or "TQM" of a given manufacturing process. This approach was developed by W. Edwards Deming in his book *Out of the Crisis*[32] and has been applied to the "process" of congenital heart surgery for improving outcomes after operative intervention for transposition of the great vessels.[33] Quality improvement programs in transfusion practices, aimed at educating physicians and improving their problem-solving capabilities, should eventually lower the incidence of excessive blood transfusion after surgery.

Drug-Related Causes

Aspirin. The pathogenesis of severe bleeding after CPB has been attributed to platelet dysfunction.[34,35] Modern platelet function testing has suggested that no intrinsic platelet defect arises from routine CPB.[36,37] It seems likely that interaction of platelets with other blood cell elements, with fibrinolysis products, or with heparin may be responsible for the CPB-induced platelet-related hemostatic

TABLE I. Guidelines for Reducing Homologous Blood Transfusion

Bleeding after Cardiopulmonary Bypass

- Therapy is directed to specific coagulation or platelet disorders.
- Transfusion may need to be given on the basis of clinical evaluation before laboratory data are available.
- Thrombocytopenia (<100,000/µL) with microvascular bleeding is indication for platelet transfusion.
- Plasma transfusion is indicated to replace suspected or documented multiple clotting factor deficiency.
- Cryoprecipitate should be used for hypofibrinogenemia (<100 mg/dL).
- Massive transfusion (more than 1 patient blood volume) should be the most common setting for multiple non-RBC component therapy.
- Real-time availability of laboratory data is recommended to allow rational use of component therapy.

Blood Conservation

- No transfusion is indicated unless there is evidence of clinical bleeding. (Transfusion should not be given in response to isolated abnormal laboratory test.)
- Multiple blood conservation measures are more likely to be successful than a single measure.
- Institutional protocol with TQM[32] problem-solving approach is best, enlisting surgeons, blood bank personnel, anesthesiologists, perfusionists, etc.

Measures *Not* Indicated

- Designated donor blood transfusions.
- Prophylactic plasma or platelet transfusions.
- Platelet transfusion for thrombocytopenia without microvascular bleeding.

RBC = red blood cell; TQM = total quality management abnormality. Nonetheless, most blood transfusion consensus guidelines (Table I) have been formulated on the assumption that CPB creates an intrinsic qualitative platelet function defect.

If platelet dysfunction is created by CPB, it seems logical that drugs that interfere with platelet aggregation or adhesion would alter postoperative hemostasis adversely and contribute to excessive blood transfusion. Aspirin has been shown to irreversibly inhibit platelet cyclooxygenase and limit the platelet release reaction.[38] In 1988, we showed that aspirin ingestion before CABG resulted in excessive postoperative blood transfusion.[39] Since then, several important observations have been made concerning the effects of preoperative aspirin ingestion. In 1990, the results of a large cooperative trial[40] of aspirin use before CABG confirmed that more blood loss and more transfusion requirements occurred in patients given preoperative aspirin. This study[40] showed that although aspirin predisposes patients to postoperative bleeding, it also confers beneficial effects on intermediate-term graft patency. This knowledge has resulted in an increase, rather than a decrease, in preoperative aspirin administration. We believe that postoperative bleeding in aspirin users is generally controllable; therefore, we do not delay operation because of recent aspirin use, except for occasional cases of patients with very prolonged preoperative bleeding times, or other high-risk situations such as difficult reoperative surgery.

There is still a subset of aspirin users who have substantial bleeding problems after CPB. An important observation in our original study[39] was that approximately 15% of patients given preoperative aspirin had an abnormally prolonged preoperative bleeding time and had to be withdrawn from the randomized part of the study. This has proved to be a consistent finding.[41] Between 15% and 20% of patients who ingest aspirin have an abnormally prolonged bleeding time of greater than 10 minutes and are considered aspirin hyperresponders. Preoperative bleeding times are useful in identifying the high-risk subset of aspirin users who might benefit from any of several blood conservation interventions.

Progress has been made toward identifying the aspirin-related defect in coagulation after CPB and explaining the phenomenon of aspirin hyperresponsiveness. Cyclooxygenase (COX) has been shown to exist in at least 2 isoforms, termed COX-1 and COX-2.[42-44] Both forms are inhibited by aspirin but to different extents; COX-1 is much more sensitive to aspirin inhibition than is COX-2 in most tissues studied.[45-47] This suggests that the effect of aspirin depends on the relative amounts of the COX isoenzymes in a given patient.

Postoperative hemostasis is undoubtedly the result of interaction between tissue and blood cell components, with plasma factors, platelets, white cells, and endothelial cells all contributing to successful control of bleeding.[37,47,48] Therefore, imbalances in the expression of COX-1 and COX-2 in any or all of these components may alter postoperative hemostasis. From a practical standpoint, aspirin hyperresponsiveness is probably related to an imbalance in COX isoforms that allows anticoagulant factors such as prostacyclin production to predominate in select individuals after operation. Several investigators have found that, because of the molecular heterogeneity in the cyclooxygenase enzyme system, aspirin use does not increase homologous blood transfusion after elective CABG.[49,50] A better understanding of the way in which aspirin alters the cellular components of hemostasis at the molecular level will eventually provide clinical benefit by reducing blood transfusion in high-risk patients.

Heparin. At present, heparin is the most widely used anticoagulant for cardiac surgery. Heparin exerts its anticoagulant effect by accelerating the formation of a molecular complex between antithrombin III and the serine proteases of the coagulation system, especially thrombin. The clotting and platelet aggregation functions of thrombin are greatly reduced in the presence of the heparin-thrombin-antithrombin III complex. It is important to note that prothrombin activation and thrombin activity are not completely inhibited by heparin during cardiac procedures: elevated amounts of activated thrombin are present at the end of CPB.[51-53] This suggests that thrombin bound to fibrin or synthetic surfaces is resistant to antithrombin III–heparin inhibition and is therefore able to facilitate further thrombin generation. The ongoing thrombin activation that occurs during CPB consumes clotting factors, activates platelets, and may contribute to excessive blood use after CPB. Because of its inability to completely prevent thrombin activation, heparin may not be the ideal anticoagulant for CPB.[54] Other thrombin or platelet inhibitors, such as dermatan sulfate,[54] thrombin aptamer,[55] low-molecular-weight heparins,[56] synthetic thrombin inhibitor peptides,[57] recombinant hirudin (a leach protein),[58] and even certain viper venoms[59] have undergone limited preclinical and clinical trials as anticoagulants for CPB and may prove useful in the future. One important advantage of heparin use is the ready availability of a neutralizing agent, protamine. Other antithrombins do not have comparable antidotes to allow easy reversal of the anticoagulant effect.

An important shortcoming of heparin is its ability to inhibit platelet function and increase fibrinolysis independent of CPB.[60,61] Heparin appears to prolong the bleeding time, increase the products of fibrin degradation,[60] and cause excessive bleeding in certain patients undergoing CPB.[61,62] Studies have suggested that increased use of heparin during CPB results in increased blood transfusion or abnormalities in coagulation parameters after heparin neutralization, post-CPB.[61-64] The mechanism of this effect may be related to the presence of heparin-binding proteins that are capable of sequestering heparin and allowing slow release of heparin into the circulation after CPB[65] or to the direct toxic effects of heparin on platelets and the fibrinolytic system.[60-62] The resulting coagulation abnormality may contribute to excessive postoperative blood transfusion.

Antithrombin III (AT III) levels decrease during CPB,[66] which may affect intraoperative thrombin generation. In 1 clinical trial, supplementation of the CPB prime with AT III resulted in decreased thrombin activation during CPB.[66] These results suggest that AT III reduces the activation of the coagulation cascade and may limit postoperative blood transfusion. Since commercial preparations of AT III are available that have no risk of disease transmission, this drug may be a reasonable candidate for blood conservation intervention. However, this hypothesis needs to be tested in a larger controlled clinical setting.

Procedure-Related Causes

Several procedure-related events are undoubtedly responsible, at least in part, for excessive postoperative blood transfusion. Perhaps the most important factor is the type of operation performed: CABG, valve procedures, or the 2 in combination; other complex procedures (valve conduit, double valve replacement, arch aneurysm repair, etc); or reoperation. Procedures that involve combined interventions are more frequently associated with excessive blood transfusion than is isolated CABG.[17] This is true for both first-time procedures and reoperations. Results at our institution support this contention (Fig. 3). An important conclusion from these findings is that patients with low RBCVOL who undergo a procedure other than CABG are at especially high risk of excessive postoperative blood transfusion. Moreover, the greatest postoperative blood transfusion requirements occur in patients with low RBCVOL who undergo complicated reoperative surgery, and it is in this subgroup that a successful blood conservation strategy will have the greatest impact.

One often-overlooked procedure-related event that may contribute to excessive blood product use is systemic hypothermia. Hypothermia has been shown to cause a reversible platelet function defect,[17,67-69] which is manifested by prolonged bleeding time and is associated with hyperfibrinolysis and complement activation.[69] These results emphasize the importance of restoring to normal both core and peripheral temperatures before turning to the transfusion of homologous blood products. In an effort to avoid the hemostatic abnormalities associated with systemic hypothermia, surgeons have performed warm heart surgery with cold[70] and warm[71] cardioplegia, each with good results; however, no significant improvement in the postoperative use of blood products has been shown.[71,72]

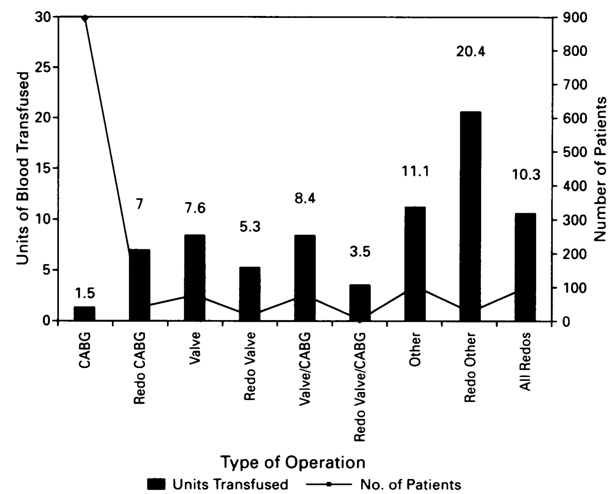

Fig. 3 Blood transfusion by operation type in 1,252 patients at Albany Medical Center during 1993.

Laboratory Diagnosis

Several authors have pointed out the poor predictive value of the usual clotting tests in screening cardiac surgical patients for the risk of excessive bleeding.[73,74] Perhaps the simplest screening technique is the estimation of the RBCVOL (blood volume times hematocrit). The blood volume can be estimated from any of several tabulations that compute blood volume based on body surface area, sex, and age. In our experience, patients with an RBCVOL of less than 1600 cc have a significantly higher risk of excessive postoperative blood transfusion, but this level of RBCVOL should be verified at each institution. In the high-risk subset (RBCVOL <1600 cc), we have found the template bleeding time to be helpful in identifying patients who are at even greater risk.[12] Patients with a bleeding time longer than 10 minutes and a low RBCVOL are at extremely high risk for receipt of excessive postoperative blood transfusion.

Many postoperative blood transfusions are given in response to a clinical suspicion of nonsurgical excessive bleeding. There is a wide variation in the way physicians respond to this clinical suspicion, because 1) there is no consensus on a diagnostic test sufficient to identify abnormal clotting or aggregation, and 2) there is limited use of real-time testing to provide instantaneous on-site measurements of platelet and clotting function. Although the predictive value of the usual clotting tests in screening cardiac surgical patients for risk of excessive bleeding is poor,[73,74] such tests can be used for both diagnosis and management of specific coagulation disorders after CPB, provided that test results are available in a timely manner.[31,75] The importance of real-time coagulation testing cannot be overemphasized, since a rational response to abnormal coagulation tests is an important method of reducing unnecessary blood transfusions and limiting excessive blood use after cardiac operations.[31] An important component of any blood conservation strategy is the ready availability of accurate diagnostic tests of coagulation and platelet function.

On-site, real-time laboratory tests for prothrombin time, partial thromboplastin time, thrombin time, fibrinogen levels, activated clotting times, heparin concentration, and platelet counts are now commercially available. Carefully constructed clinical trials are needed to test whether or not real-time coagulation testing with blood transfusion directed by abnormal test results is a cost-effective measure. It could be that the savings in blood product would more than offset the additional expense of purchasing and performing real-time coagulation tests.

Other laboratory tests have been used to detect whole-blood global coagulation abnormalities in the operating room. These include thromboelastography,[76,77] Sonoclot determinations,[78] and hemostatometry.[61,79] The main potential advantage of these tests is the real-time availability of the results on site. Clinical trials to measure the effectiveness of these global tests in guiding transfusion therapy and limiting excessive blood usage are lacking.

As discussed previously, heparin has a direct toxic effect on some of the components of hemostasis after CPB. It follows that the optimal use of heparin involves effective neutralization of prothrombin activation and limitation of the direct toxic effects on platelets and the fibrinolytic system. From a clinical viewpoint, this means avoiding excessive heparin dosage but using enough to reduce prothrombin activation to a minimal level. The activated clotting time (ACT) has been used to monitor heparin levels during and after CPB, but ACT measurements do not correlate well with plasma heparin levels.[80-82] The ACT is particularly insensitive to low plasma heparin levels. This deficiency in the ACT has led to the development and use of whole blood heparin concentration analysis using protamine titration, resulting in a measurement that correlates well with plasma heparin concentration.[82] Further studies are needed to determine whether maintaining optimal heparin levels during CPB with whole blood heparin measurements can minimize the toxic side effects of heparin and limit excessive blood transfusion.

Interventions

Reporting Results of Blood Conservation Interventions

A review of the medical literature concerning the measures used to reduce blood loss and blood transfusion after cardiac procedures yields numerous conflicting reports on the efficacy of any given blood conservation intervention (Table II). Part of the explanation for this diversity may be in the lack of uniformity and completeness in reporting the results of blood conservation interventions, as described in a recent editorial.[83] Several features of this editorial are worth emphasizing. First, studies that use postoperative chest catheter output as an index of blood volume loss are misleading, since chest tube blood loss does not necessarily correlate with postoperative blood transfusion. Second, as shown in Figure 1, the distribution of blood product transfusion is not a normal distribution; therefore, statistics that evaluate the significance of a given blood conservation intervention should use nonparametric methods rather than the Student's *t*-test or other tests that assume normal variance. Third, many of the clinical studies that describe the effects of blood conservation are not randomized, which increases the possibility of investigator bias and makes it imperative that investigators characterize completely the patients in each treatment group. Fourth, it is essential that comparisons of blood conservation interventions state explicitly the criteria used for transfusion ("transfusion triggers"), because the variability in transfusion practices of individual surgeons and in the reporting of such interventions makes comparisons difficult, and perhaps impossible, in some cases. In this review, we have attempted to be as complete and current as possible in our review of the literature. However, we have included only papers that appeared to meet most or all of the above-mentioned standards so that meaningful comparisons could be made regarding excessive postoperative blood transfusion. For consideration of the efficacy of blood conservation interventions, the sparing of postoperative blood transfusion was used as the primary measure of success.

Many authors have emphasized the importance of a multifactorial approach to conserving blood and limiting excessive transfusion.[8-11,13,16] These reports provide good evidence that a combination of blood conservation interventions is more beneficial than the sum of the individual components. Any viable strategy for limiting excessive blood transfusion after cardiac procedures should identify the institution-specific blood conservation interventions that are helpful and apply these interventions in combination. This multifactorial approach is especially valuable for high-risk patients.

Drug Interventions

Aprotinin. Of all the drugs used to minimize postoperative bleeding and reduce blood transfusion, aprotinin has proved to be the most successful. To our knowledge there have been no published reports suggesting that high-dose aprotinin does not limit postoperative bleeding. No other blood conservation drug has a comparable record (see Table II).

Although there can be little doubt about aprotinin's efficacy in limiting excessive blood transfusion,[84] there is a lack of consensus concerning the routine use of this drug for all cardiac procedures requiring CPB. At present there are mixed reports regarding the benefit of low-dose regimens as opposed to the high-dose (Hammersmith[84]) regimen in limiting blood loss and preventing blood transfusion.[85,86] The cost of a full-dose aprotinin regimen is substantial: equivalent to the cost of about 8 to 10 units of blood. In addition, the use of aprotinin in operations that may involve periods of circulatory arrest must be viewed with caution, since aprotinin may predispose the patient to microvascular sludging and thrombosis.[87] Initial studies using aprotinin in reoperative coronary surgery suggested that aprotinin was associated with decreased early graft patency.[88] Since then, 3 randomized studies have shown that there is no significant difference in early graft patency between patients given aprotinin and those in a control group.[89-91] A potentially beneficial feature of aprotinin is its ability to act as an antiprotease in the microcirculation. Indeed, the drug may ultimately be used for stabilizing the micro-

TABLE II. Efficacy of Perioperative Blood Conservation Interventions

	Efficacy of Intervention (Reference Number)		
Intervention	**Positive**	**Negative**	**Consensus**
Drugs			
Aprotinin	84, 87, 88, 90	—	+++
ε-Aminocaproic acid and tranexamic acid	94, 96, 97, 101	95, 98, 99, 100	+/–
Erythropoietin	103, 104, 105, 106	102	++
Desmopressin	107	108, 109, 110, 111, 112, 113, 114	–
Devices			
Heparin-bonded circuits	119, 120, 121	118	+/–
PRP saver	122, 123, 124	125, 126, 127, 128	+/–
Cell saver	129, 130, 131	132, 133, 134	+/–
Circulatory pumps	137	—	*
Other			
Shed blood reinfusion	139, 140, 141	131, 142, 143, 144, 145, 146, 147, 148	–
Blood pooling (hemodilution)	10, 22, 149, 150, 152	122	++
Predonation	103, 105, 155, 156, 157, 158, 159	162	++
Pump salvage	136, 164, 165, 166	—	+++
Hemofiltration	132, 135	133, 134	+/–

+++ = all positive
++ = mostly positive
+/– = mixed
– = mostly negative

PRP = platelet-rich plasma

*Insufficient data

circulation and limiting the total body inflammatory response after CPB, especially in high-risk patients.[92,93]

Antifibrinolytics Other Than Aprotinin. While aprotinin is an irreversible inhibitor of the fibrinolytic system and other serum proteases, other drugs are available that are competitive inhibitors of plasmin. ε-Aminocaproic acid and tranexamic acid are 2 such inhibitors that have been used in several clinical studies with mixed results.[94-101] Most positive studies show some improvement in chest drainage but lesser effects on blood product use. High doses of tranexamic acid may be associated with an increased rate of perioperative myocardial infarction; therefore, the high-dose regimen is not recommended.[95]

Erythropoietin. Recombinant human erythropoietin has been used to increase the red cell mass in patients before surgery.[102-105] This drug can be administered subcutaneously[104] and is especially effective in anemic patients.[102] The main side effect is systolic hypertension; another disadvantage is that the dosing regimen requires several doses to be given over a 2- to 3-week interval. Erythropoietin has been used to augment patients' red cell mass in preparation for autologous blood predonation.[102,103] A recent study in patients undergoing orthopedic procedures found that erythropoietin provided no clinical benefit to autologous blood donors unless the patients had preoperative anemia.[102] A logical extension of these findings is that patients who are at high risk for excessive postoperative blood transfusion may benefit from a delay of their cardiac procedures while erythropoietin therapy is given to replenish red cell mass. Of course, it is not possible to delay operation in all patients; however, when possible, this therapy might allow less blood use and lead to reduced postoperative morbidity. Erythropoietin may also prove to be extremely useful in Jehovah's Witness patients who have preoperative anemia.[106]

Desmopressin. After initial enthusiasm for desmopressin as an agent that limited blood transfusion,[107] several reports showed no clinical benefit from desmopressin after cardiac procedures.[108-114] Because of the overwhelming preponderance of negative studies appearing in the literature, desmopressin cannot be recommended for use in limiting postoperative blood transfusion after cardiac surgery.

Interventions with Devices

Heparin-Bonded Circuits. Many vasoactive substances are released into the circulation as a result of CPB; the combination of compensatory changes in hemostasis, fluid shifts, and cellular and hormonal defense reactions has been termed the "whole body inflammatory response."[115-117] In an effort to limit the release of these inflammatory mediators and decrease postoperative bleeding, perfusion circuits coated with heparin have been introduced into clinical practice. This introduction has occurred with surprisingly little efficacy testing, most likely because governmental regulations covering perfusion devices are much less stringent than those for implantable devices (e.g., valves and pacemakers).

Heparin is bound to the CPB circuit by 2 different methods. One (Carmeda-bonded) involves endpoint attachment of heparin to the synthetic surface and leaves the active site of heparin exposed and capable of binding AT III. The other (Duraflo II) involves binding of heparin to the synthetic surface in a manner such that the active site is not exposed and is not capable of binding AT III. Multiple preclinical studies have been performed using both of these circuits, and each seems capable of altering some aspects of the inflammatory response and preserving hemostatic integrity. However, only 4 clinical studies have appeared in the literature[118-121] that ask whether or not heparin coating of the oxygenator and tubing can reduce blood utilization. One of these studies,[118] which used non-AT–III-active circuits (Duraflo II), found no benefit in blood conservation, although there was biochemical evidence that platelet activation was decreased. Three other studies[119-121] using AT–III-active circuits suggested that blood loss was decreased; however, the numbers of patients enrolled were small. Therefore, it is difficult to draw firm conclusions regarding the effect of heparin-bonded circuits on excessive blood transfusion based on these studies.[119-121] It may be that heparin coating of the bypass circuit has a secondary benefit of allowing reduced systemic doses of heparin, thus limiting CPB-induced damage to hemostasis. This is an area where cost–benefits must be carefully analyzed, since heparin-bonded circuits usually add to the cost of CPB.

Preoperative Platelet-Rich Plasma Harvest. Several well-designed clinical trials have been carried out using commercially available centrifugation apparatuses that allow harvest of autologous platelet-rich plasma before operation, followed by reinfusion after operation. The theoretical advantage of this approach is that platelets and plasma components are spared the exposure to CPB, and more hemostatically active platelets are available after operation. The findings of these clinical trials have been mixed (Table II): several studies have reported favorable results;[122-124] others have shown no benefit.[125-128] At present, the use of plateletpheresis as a routine blood conservation method is questionable, since this technology adds additional expense to CPB without substantial proven benefit. Certain high-risk patients may benefit from this technology as part of a multifaceted approach.[122]

Cell Saving. Several methods of intraoperative blood salvage are commercially available and have been tested in clinical trials. Perhaps the most widely used of these salvaging techniques involves centrifugation of blood that has been suctioned from the operative field and mixed with heparin. The centrifuged product (mainly red cells) is then returned to the patient minus platelets and clotting proteins. The advantage of this technique is that it can be used throughout the operative period, from before heparin administration into the early postoperative period. The same setup can be used to salvage blood remaining in the oxygenator after CPB, and to wash red cells shed from the mediastinum into chest tube collection devices. Several studies have found that this technique can result in decreased blood transfusion,[129-131] while others have not found significant benefit.[132-134] The additional cost and the doubtful benefits of cell centrifugation suggest that the use of a cell saving device may not be cost-effective.[130] Other techniques, such as direct infusion or ultrafiltration, do not involve as much additional cost as the cell saving apparatus and are equally effective in limiting postoperative transfusion.[135] In addition, because centrifugation is included with the use of the cell saving device, there can be a loss of serum proteins in certain patients with low blood volume and hypoproteinemia.[134]

Newer Pump Devices. Other devices that are in earlier stages of clinical development may prove useful in limiting postoperative transfusion. These devices include the Hemopump® Cardiac Assist System (Johnson & Johnson Interventional Systems, Inc.; Rancho Cordova, California) and the centrifugal pump. The Hemopump is a high-speed rotary cardiac assist device that has been used to support the circulation during coronary revascularization.[136] This new technology holds great promise for reducing blood transfusion, since it avoids many of the drawbacks of CPB, including high-dose heparin therapy and cardioplegic arrest. At present, open cardiac procedures such as valve operations and ascending aortic aneurysm surgery cannot be performed using the Hemopump device. The ultimate application of the Hemopump awaits further clinical investigation.

Centrifugal pumps have been used to assist the circulation during CPB and after failure to wean from CPB. With regard to blood conservation, very few clinical studies have shown significant harm or benefit from these devices, despite claims from manufacturers that these devices may limit postoperative blood transfusion. Perhaps the biggest potential advantage of centrifugal pumps will prove to be the minimal heparin dose required when these devices are used.[137] Additional clinical information is needed concerning the efficacy of these newer devices in limiting postoperative blood transfusion.

Other Interventions

Reinfusion of Shed Mediastinal Blood. Direct autotransfusion of shed mediastinal blood after CPB is an established method of salvaging red cells and some plasma components, being one of the earliest methods of blood conservation used.[138] Several commercial systems facilitate the collection and reinfusion of mediastinal blood, without washing, directly into patients by intravenous infusion. Despite the extent of clinical commercial interest that exists, there is no consensus regarding the efficacy of this blood conservation method. Several reports suggest significant clinical benefit in limiting postoperative blood transfusion.[139-141] Others suggest no benefit[131,142-148] or even possible harm from reinfusion of toxic fibrinolytic products into the blood stream,[143,144,147] especially in aspirin users[143] or in patients who are given large amounts of autotransfused mediastinal blood.[144] In view of the increased cost and potentially harmful effects associated with reinfusion of shed mediastinal blood, this technique cannot be recommended for routine use in patients expected to require excessive blood transfusion after operation.

Autologous Blood Pooling (Hemodilution). One of the earliest successful methods of blood conservation used in cardiac surgery was hemodilution with pooling of autologous blood before CPB and reinfusion after bypass.[149-151] This method has stood the test of time in that few, if any, harmful side effects have been reported, and recent studies with newer perfusion equipment and presumably sicker patients have confirmed the beneficial effects of "blood pooling."[10,22,152-154] The addition of hypertonic saline solution to the CPB priming solution seems to improve the oxygen-carrying capacity in the hemodiluted state.[153] This method may have limited usefulness in the patient with significant preoperative anemia or diminished blood volume, which is often present in the high-risk subset of patients undergoing CPB.[122] Nonetheless, this technique is an inexpensive, safe, and usually applicable method to limit blood transfusion after CPB. Care must be taken to avoid significant preoperative hypotension from hypovolemia, since this may cause ischemic changes in patients with compromised ventricular function.[154]

Autologous Predonation. Numerous reports extol the worth of predonation of autologous blood in order to avoid use of homologous blood transfusion during cardiac procedures.[105,155-159] The addition of subcutaneous recombinant human erythropoietin to the preoperative regimen has enhanced the efficacy of this technique in reducing the need for transfusion in cardiac patients.[103,105,158] For a blood conservation intervention that is so widely accepted as beneficial, it is surprising that so few patients presenting for cardiac operations actually participate in a predonation program. During 1993, only 61 of 1,252 (4.9%) patients undergoing open heart surgery at our institution were able to predonate a minimum of 1 unit of blood (Fig. 4). Surveys of various autologous predonation programs have found consistent underutilization of this modality.[160,161] In most cases, cardiologists and surgeons seem unwilling to delay operation to allow predonation. The reasons for this disinclination are unclear, but may involve both a perception by physicians that the technique has risks[162] and an unfamiliarity with the indications for and benefits of predonation.[163] The limitations of predonation include the need for delay of operation and the uncertain applicability in the highest-risk patients who may have preoperative decreased RBCVOL. Nevertheless, autologous predonation is an important intervention to limit excessive postoperative blood transfusion.

Pump Salvage. Intraoperative salvage of blood from the oxygenator circuit (pump salvage) is a very cost-effective blood conservation measure that has been shown to decrease homologous blood requirements with very few risks.[135,164-166] The risks associated with reinfusion of shed mediastinal blood (see above) are not apparent with reinfusion of oxygenator blood immediately after CPB. This is an important distinction, since it appears that reinfusion of shed mediastinal blood that has been exposed to the proteolytic enzymes within the pericardium causes a hemostatic defect after CPB.[143,144,147]

Hemofiltration during CPB. Hemofiltration devices are used in series with the CPB circuit to concentrate the diluted pump blood and to allow reinfusion of a concentrated whole blood product. This technique has been compared both to cell saving[133-135] and to direct reinfusion of blood remaining in the oxygenator circuit.[135] Hemofiltration has proved to be better than use of a cell saving device but equivalent to direct reinfusion (termed pump salvage in the present review). On the basis of these studies, incurring the additional expense of hemofiltration devices does not seem reasonable when pump salvage is equally effective and less costly. Hemofiltration devices have a theoretical advantage, in that the toxic products of CPB (such as some cytokines) may be removed by these devices.[167] More research needs to be performed before hemofiltration can be recommended to limit excessive blood transfusion.

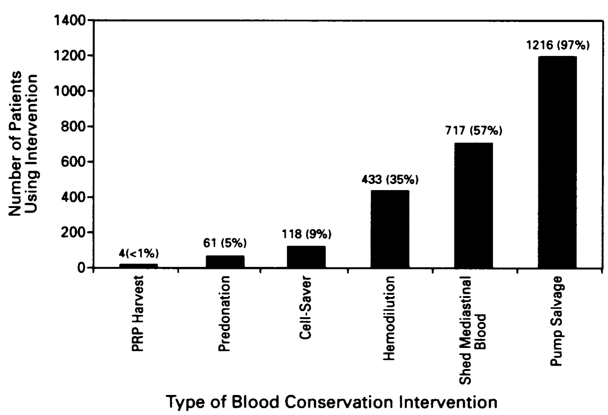

Fig. 4 *Blood conservation interventions used in 1,252 patients undergoing operation at Albany Medical Center in 1993.*

Conclusions: Treatment Strategy

Standard perioperative blood conservation measures have not been totally successful in treating the high-risk subset of patients who require excessive blood transfusion; new approaches still need to be developed (Table III). Understanding that preoperative anemia and decreased blood volume predispose patients to excessive postoperative blood transfusion is a necessary first step. If a patient has diminished blood volume from anemia or decreased bone marrow reserves before surgery, then intraoperative

TABLE III. Proposed Strategy for Limiting Excessive Postoperative Blood Transfusion

Recognize Causes of Excessive Transfusion

- Consider impact of preoperative anemia, low RBCVOL, procedure type, etc.
- Alter unfavorable preoperative variables where possible (delay operation, withdraw aspirin, encourage erythropoietin-aided predonation, etc.).

Establish a TQM[32] Approach to Excessive Blood Transfusion

- Monitor institution transfusion practices.
- Emphasize physician education.
- Introduce transfusion algorithms.

Combine Blood Conservation Measures in High-Risk Patients

- Use a selective multi-factorial approach for high-risk patients.
- Consider aprotinin, pump salvage, and blood pooling with hemodilution as important components.
- Remember often-overlooked features, including optimizing heparin dose, adequate post-CPB rewarming, and identifying aspirin hyperresponders.
- Use real-time laboratory testing in operating room.

Continually Reassess Blood Product Use

- Obtain frequent audits of transfusion practices.
- Perform a cost–benefit analysis of each intervention.

CPB = cardiopulmonary bypass; RBCVOL = red blood cell volume; TQM = total quality management and postoperative blood conservation measures will meet with limited success and may even prove harmful. For patients in whom delay of operation is possible, it may be best to augment red blood cell volume with erythropoietin and to withhold aspirin therapy before undertaking operative intervention. Patients in the high-risk subset may be particularly susceptible to the effects of platelet-active drugs such as aspirin. Preoperative screening of these patients with evaluation of bleeding time followed by delay of operation in certain aspirin hyperresponders may limit excessive blood transfusion.

The next step in reducing excessive blood use should be taken at the institutional level, using the principles of total quality management (TQM). This approach entails first identifying and quantitating the transfusion practices at a given institution, then involving all of the critical health-care providers. Transfusion algorithms may prove useful in this endeavor to limit excessive blood transfusion.

In addition, after the high-risk patient population has been identified, appropriate, institution-specific blood conservation measures should be used selectively in this group. For perioperative blood conservation, it is important to establish a multifaceted approach, including institution-proven modalities and aprotinin administration in selected patients.

Finally, continual reassessment of the institution's transfusion practices is essential, including frequent audits and cost–benefit analyses, with the objective of adding new features and removing unhelpful techniques. These steps should bring us closer to the ultimate goal of reducing the excessive blood transfusion that occurs in high-risk cardiac surgical patients.

References

1. Ward JW, Holmberg SD, Allen JR, Cohn DL, Critchley SE, Kleinman SH, et al. Transmission of human immunodeficiency virus (HIV) by blood transfusions screened as negative for HIV antibody. N Engl J Med 1988;318:473-8.
2. Collins JD, Bassendine MF, Codd AA, Collins A, Ferner RE, James OF. Prospective study of post-transfusion hepatitis after cardiac surgery in a British centre. Br Med J (Clin Res Ed) 1983;287:1422-4.
3. Pollock R, Ames F, Rubio P, Jones J, Reuben J, Wong W, et al. Protracted severe immune dysregulation induced by cardiopulmonary bypass: a predisposing etiologic factor in blood transfusion-related AIDS? J Clin Lab Immunol 1987;22:1-5.
4. Murphy PJ, Connery C, Hicks GL Jr, Blumberg N. Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. J Thorac Cardiovasc Surg 1992;104:1092-9.
5. Breyer RH, Engelman RM, Rousou JA, Lemeshow S. Blood conservation for myocardial revascularization. Is it cost effective? J Thorac Cardiovasc Surg 1987;93:512-22.
6. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. Am J Med 1993;94:509-14.
7. Graves EJ. National hospital discharge survey: annual summary, 1991. Vital Health Stat [13] 1993;(114):1-62.
8. Tyson GS, Sladen RN, Spainhour V, Savitt MA, Ferguson TB Jr, Wolfe WG. Blood conservation in cardiac surgery. Preliminary results with an institutional commitment. Ann Surg 1989;209:736-42.
9. LoCicero J III, Massad M, Gandy K, Sanders JH Jr, Hartz RS, Frederiksen JW, et al. Aggressive blood conservation in coronary artery surgery: impact on patient care. J Cardiovasc Surg (Torino) 1990;31:559-63.
10. Jones JW, Rawitscher RE, McLean TR, Beall AC Jr, Thornby JI. Benefit from combining blood conservation measures in cardiac operations. Ann Thorac Surg 1991;51:541-6.
11. Scott WJ, Rode R, Castlemain B, Kessler R, Follis F, Pett SB, et al. Efficacy, complications, and cost of a comprehensive blood conservation program for cardiac operations. J Thorac Cardiovasc Surg 1992;103:1001-7.
12. Ferraris VA, Gildengorin V. Predictors of excessive blood use after coronary artery bypass grafting. A multivariate analysis. J Thorac Cardiovasc Surg 1989;98:492-7.
13. Scott WJ, Kessler R, Wernly JA. Blood conservation in cardiac surgery. Ann Thorac Surg 1990;50:843-51.
14. Bracey AW, Radovancevic R. The hematologic effects of cardiopulmonary bypass and the use of hemotherapy in coronary artery bypass grafting. Arch Pathol Lab Med 1994;118:411-6.
15. Goodnough LT, Johnston MF, Toy PT. The variability of transfusion practice in coronary artery bypass surgery. Transfusion Medicine Academic Award Group. JAMA 1991;265:86-90.
16. Cosgrove DM, Loop FD, Lytle BW, Gill CC, Golding LR, Taylor PC, et al. Determinants of blood utilization during myocardial revascularization. Ann Thorac Surg 1985;40:380-4.
17. Hardy JF, Perrault J, Tremblay N, Robitaille D, Blain R, Carrier M. The stratification of cardiac surgical procedures according to use of blood products: a retrospective analysis of 1480 cases. Can J Anaesth 1991;38:511-7.
18. Goodnough LT, Soegiarso RW, Geha AS. Blood lost and blood transfused in coronary artery bypass graft operation as implications for blood transfusion and blood conservation strategies. Surg Gynecol Obstet 1993;177:345-51.
19. Tsai TP, Chaux A, Kass RM, Gray RJ, Matloff JM. Aortocoronary bypass surgery in septuagenarians and octogenarians. J Cardiovasc Surg (Torino) 1989;30:364-8.
20. Goodnough LT, Vizmeg K, Riddell J IV, Soegiarso RW. Discharge haematocrit as clinical indicator for blood transfusion audit in surgery patients. Transfus Med 1994;4:35-44.
21. Czer LSC, Shoemaker WC. Optimal hematocrit value in critically ill postoperative patients. Surg Gynecol Obstet 1978;147:363-8.
22. Mathru M, Kleinman B, Blakeman B, Sullivan H, Kumar P, Dries DJ. Myocardial metabolism and adaptation during extreme hemodilution in humans after coronary revascularization. Crit Care Med 1992;20:1420-5.
23. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. Ann Intern Med 1992;116:393-402.
24. Goodnough LT, Johnston MFM, Ramsey G, Sayers MH, Eisenstadt RS, Anderson KC, et al. Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. Transfusion Practices Committee of the American Association of Blood Banks. Ann Thorac Surg 1990;50:675-83.
25. Contreras M, Ala FA, Greaves M, Jones J, Levin M, Machin SJ, et al. Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. Transfus Med 1992;2:57-63.

26. Consensus conference. Perioperative red blood cell transfusion. JAMA 1988;260:2700-3.
27. Consensus conference. Fresh-frozen plasma. Indications and risks. JAMA 1985;253:551-3.
28. Consensus conference. Platelet transfusion therapy. JAMA 1987;257:1777-80.
29. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. J Thorac Cardiovasc Surg 1992;104:307-14.
30. Surgenor DM, Wallace EL, Churchill WH, Hao SH, Chapman RH, Collins JJ Jr. Red cell transfusions in coronary artery bypass surgery (DRGs 106 and 107) [published erratum appears in Transfusion 1992;32:876]. Transfusion 1992;32:458-64.
31. Despotis GJ, Grishaber JE, Goodnough LT. The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. Transfusion 1994;34:290-6.
32. Deming WE. Out of the crisis. Cambridge: Massachusetts Institute of Technology, Center for Advanced Engineering Study, 1982:465-74.
33. de Leval MR, Francois K, Bull C, Brawn W, Spiegelhalter D. Analysis of a cluster of surgical failures. Application to a series of neonatal arterial switch operations. J Thorac Cardiovasc Surg 1994;107:914-24.
34. Woodman RC, Harker LA. Bleeding complications associated with cardiopulmonary bypass. Blood 1990;76:1680-97.
35. Harker LA, Malpass TW, Branson HE, Hessel EA II, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective α-granule release. Blood 1980;56:824-34.
36. Kestin AS, Valeri CR, Khuri SF, Loscalzo J, Ellis PA, MacGregor H, et al. The platelet function defect of cardiopulmonary bypass. Blood 1993;82:107-17.
37. Reich H, Ferraris VA, Ferraris SP, Rodriguez E, Huang M, Gupta A, et al. The hemostatic defect after cardiopulmonary bypass is not an intrinsic platelet function defect. Surg Forum 1994;45:252-5.
38. Picot D, Loll PJ, Garavito RM. The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. Nature 1994;367:243-9.
39. Ferraris VA, Ferraris SP, Lough FC, Berry WR. Preoperative aspirin ingestion increases operative blood loss after coronary artery bypass grafting. Ann Thorac Surg 1988;45:71-4.
40. Sethi GK, Copeland JG, Goldman S, Moritz T, Zadina K, Henderson WG. Implications of preoperative administration of aspirin in patients undergoing coronary artery bypass grafting. Department of Veterans Affairs Cooperative Study on Antiplatelet Therapy. J Am Coll Cardiol 1990;15:15-22.
41. Fiore LD, Brophy MT, Lopez A, Janson P, Deykin D. The bleeding time response to aspirin. Identifying the hyperresponder. Am J Clin Pathol 1990;94:292-6.
42. O'Banion MK, Sadowski HB, Winn V, Young DA. A serum- and glucocorticoid-regulated 4-kilobase mRNA encodes a cyclooxygenase-related protein. J Biol Chem 1991;266:23261-7.
43. Hla T, Neilson K. Human cyclooxygenase-2 cDNA. Proc Natl Acad Sci U S A 1992;89:7384-8.
44. O'Neill GP, Ford-Hutchinson AW. Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues. FEBS Lett 1993;330:156-60.
45. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci U S A 1993;90:11693-7.
46. Meade EA, Smith WL, DeWitt DL. Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal anti-inflammatory drugs. J Biol Chem 1993;268:6610-4.
47. Vane J. Towards a better aspirin. Nature 1994;367:215-6.
48. Ferraris VA, Rodriquez E, Ferraris SP, Huang M, Gupta A, Bennett JA, et al. Platelet aggregation abnormalities after cardiopulmonary bypass. Blood 1994;83:299-301.
49. Reich DL, Patel GC, Vela-Cantos F, Bodian C, Lansman S. Aspirin does not increase homologous blood requirements in elective coronary bypass surgery. Anesth Analg 1994;79:4-8.
50. Rawitscher RE, Jones JW, McCoy TA, Lindsley DA. A prospective study of aspirin's effect on red blood cell loss in cardiac surgery. J Cardiovasc Surg (Torino) 1991;32:1-7.
51. Brister SJ, Ofosu FA, Buchanan MR. Thrombin generation during cardiac surgery: is heparin the ideal anticoagulant? Thromb Haemost 1993;70:259-62.
52. Boisclair MD, Lane DA, Philippou H, Esnouf MP, Sheikh S, Hunt B, et al. Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood 1993;82:3350-7.
53. Slaughter TF, LeBleu TH, Douglas JM Jr, Leslie JB, Parker JK, Greenberg CS. Characterization of prothrombin activation during cardiac surgery by hemostatic molecular markers. Anesthesiology 1994;80:520-6.
54. Brister SJ, Ofosu FA, Heigenhauser GJF, Gianese F, Buchanan MR. Is heparin the ideal anticoagulant for cardiopulmonary bypass? Dermatan sulphate may be an alternate choice. Thromb Haemost 1994;71:468-73.
55. DeAnda A Jr, Coutre SE, Moon MR, Vial CM, Griffin LC, Law VS, et al. Pilot study of the efficacy of a thrombin inhibitor for use during cardiopulmonary bypass. Ann Thorac Surg 1994;58:344-50.
56. Bagge L, Wahlberg T, Holmer E, Tyden H, Nystrom SO, Malm T. Low-molecular-weight heparin (Fragmin) versus heparin for anticoagulation during cardiopulmonary bypass in open heart surgery, using a pig model. Blood Coagul Fibrinolysis 1994;5:265-72.
57. Chomiak PN, Walenga JM, Koza MJ, Reilly TM, Turlapathy P, Pifarre R. Investigation of a thrombin inhibitor peptide as an alternative to heparin in cardiopulmonary bypass surgery. Circulation 1993;88(5 Pt 2):II-407-12.
58. Walenga JM, Bakhos M, Messmore HL, Fareed J, Pifarre R. Potential use of recombinant hirudin as an anticoagulant in a cardiopulmonary bypass model. Ann Thorac Surg 1991;51:271-7.
59. Musial J, Niewiarowski S, Rucinski B, Stewart GJ, Cook JJ, Williams JA, et al. Inhibition of platelet adhesion to surfaces of extracorporeal circuits by disintegrins. RGD-containing peptides from viper venoms. Circulation 1990;82:261-73.
60. Khuri S, Valeri CR, Loscalzo J, et al. Heparin causes platelet dysfunction and increases fibrinolysis before the institution of cardiopulmonary bypass. Presented at the 31st annual meeting of the Society of Thoracic Surgeons; 1995 Jan 30-Feb 1; Palm Springs, CA. Ann Thorac Surg. In Press.
61. John LCH, Rees GM, Kovacs IB. Inhibition of platelet function by heparin. An etiologic factor in postbypass hemorrhage. J Thorac Cardiovasc Surg 1993;105:816-22.
62. Iverson LIG, Duhaylongsod FG, Young JN, Ecker RR, Ennix CL Jr, Moretti RL, et al. Porcine heparin increases postoperative bleeding in cardiopulmonary bypass patients. Cardiovasc Drugs Ther 1990;4:269-72.
63. Gravlee GP, Haddon WS, Rothberger HK, Mills SA, Rogers AT, Bean VE, et al. Heparin dosing and monitoring for cardiopulmonary bypass. A comparison of techniques with measurement of subclinical plasma coagulation. J Thorac Cardiovasc Surg 1990;99:518-27.
64. Gravlee GP, Rogers AT, Dudas LM, Taylor R, Roy RC, Case LD, et al. Heparin management protocol for cardiopulmo-

nary bypass influences postoperative heparin rebound but not bleeding. Anesthesiology 1992;76:393-401.
65. Teoh KHT, Young E, Bradley CA, Hirsh J. Heparin binding proteins. Contribution to heparin rebound after cardiopulmonary bypass. Circulation 1993;88(5 Pt 2):II-420-5.
66. Hashimoto K, Yamagishi M, Sasaki T, Nakano M, Kurosawa H. Heparin and antithrombin III levels during cardiopulmonary bypass: correlation with subclinical plasma coagulation. Ann Thorac Surg 1994;58:799-805.
67. Michelson AD, MacGregor H, Barnard MR, Kestin AS, Rohrer MJ, Valeri CR. Reversible inhibition of human platelet activation by hypothermia in vivo and in vitro. Thromb Haemost 1994;71:633-40.
68. Valeri CR, Khabbaz K, Khuri SF, Marquardt C, Ragno G, Feingold H, et al. Effect of skin temperature on platelet function in patients undergoing extracorporeal bypass. J Thorac Cardiovasc Surg 1992;104:108-16.
69. Khuri SF, Wolfe JA, Josa M, Axford TC, Szymanski I, Assousa S, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss. J Thorac Cardiovasc Surg 1992;104: 94-107.
70. Singh AK, Feng WC, Bert AA, Rotenberg FA. Warm body, cold heart: myocardial revascularization in 2383 consecutive patients. J Cardiovasc Surg (Torino) 1993;34:415-21.
71. Christakis GT, Koch JP, Deemar KA, Fremes SE, Sinclair L, Chen E, et al. A randomized study of the systemic effects of warm heart surgery. Ann Thorac Surg 1992;54:449-59.
72. Kavanagh BP, Mazer CD, Panos A, Lichtenstein SV. Effect of warm heart surgery on perioperative management of patients undergoing urgent cardiac surgery. J Cardiothorac Vasc Anesth 1992;6:127-31.
73. Gravlee GP, Arora S, Lavender SW, Mills SA, Hudspeth AS, Cordell AR, et al. Predictive value of blood clotting tests in cardiac surgical patients. Ann Thorac Surg 1994;58:216-21.
74. Fassin W, Himpe D, Alexander JP, Borms S, Theunissen W, Muylaert P, et al. Predictive value of coagulation testing in cardiopulmonary bypass surgery. Acta Anaesthesiol Belg 1991;42:191-8.
75. Despotis GJ, Santoro SA, Spitznagel E, Kater AM, Cox JL, Barnes P, et al. Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operation. J Thorac Cardiovasc Surg 1994;107:271-9.
76. Essell JH, Martin TJ, Salinas J, Thompson JM, Smith VC. Comparison of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1993;7:410-5.
77. Dorman BH, Spinale FG, Bailey MK, Kratz JM, Roy RC. Identification of patients at risk for excessive blood loss during coronary artery bypass surgery: thromboelastography versus coagulation screen. Anesth Analg 1993;76:694-700.
78. Stern MP, DeVos-Doyle K, Viguera MG, Lajos TZ. Evaluation of post-cardiopulmonary bypass Sonoclot signatures in patients taking nonsteroidal anti-inflammatory drugs. J Cardiothorac Anesth 1989;3:730-3.
79. Ratnatunga CP, Rees GM, Kovacs IB. Preoperative hemostatic activity and excessive bleeding after cardiopulmonary bypass. Ann Thorac Surg 1991;52:250-7.
80. Culliford AT, Gitel SN, Starr N, Thomas ST, Baumann FG, Wessler S, et al. Lack of correlation between activated clotting time and plasma heparin during cardiopulmonary bypass. Ann Surg 1981;193:105-11.
81. Metz S, Keats AS. Low activated coagulation time during cardiopulmonary bypass does not increase postoperative bleeding. Ann Thorac Surg 1990;49:440-4.
82. Despotis GJ, Summerfield AL, Joist JH, Goodnough LT, Santoro SA, Spitznagel E, et al. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations. J Thorac Cardiovasc Surg 1994; 108:1076-82.
83. Lemmer JH Jr. Reporting the results of blood conservation studies: the need for uniform and comprehensive methods. Ann Thorac Surg 1994;58:1305-6.
84. Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). J Thorac Cardiovasc Surg 1989;97:364-72.
85. Hardy JF, Desroches J, Belisle S, Perrault J, Carrier M, Robitaille D. Low-dose aprotinin infusion is not clinically useful to reduce bleeding and transfusion of homologous blood products in high-risk cardiac surgical patients. Can J Anaesth 1993;40:625-31.
86. Liu B, Belboul A, Radberg G, Tengborn L, Dernevik L, Roberts D, et al. Effect of reduced aprotinin dosage on blood loss and use of blood products in patients undergoing cardiopulmonary bypass. Scand J Thorac Cardiovasc Surg 1993; 27:149-55.
87. Sundt TM III, Kouchoukos NT, Saffitz JE, Murphy SF, Wareing TH, Stahl DJ. Renal dysfunction and intravascular coagulation with aprotinin and hypothermic circulatory arrest. Ann Thorac Surg 1993;55:1418-24.
88. Cosgrove DM III, Heric B, Lytle BW, Taylor PC, Novoa R, Golding LA, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. Ann Thorac Surg 1992;54:1031-8.
89. Havel M, Grabenwoger F, Schneider J, Laufer G, Wollenek G, Owen A, et al. Aprotinin does not decrease early graft patency after coronary artery bypass grafting despite reducing postoperative bleeding and use of donated blood. J Thorac Cardiovasc Surg 1994;107:807-10.
90. Lemmer JH Jr, Stanford W, Bonney SL, Breen JF, Chomka EV, Eldredge WJ, et al. Aprotinin for coronary bypass operations: efficacy, safety, and influence on early saphenous vein graft patency. A multicenter, randomized, double-blind, placebo-controlled study. J Thorac Cardiovasc Surg 1994;107:543-53.
91. Bidstrup BP, Underwood SR, Sapsford RN, Streets EM. Effect of aprotinin (Trasylol) on aorta-coronary bypass graft patency. J Thorac Cardiovasc Surg 1993;105:147-53.
92. Taylor KM. Improved outcome for seriously ill open heart surgery patients: focus on reoperation and endocarditis. J Heart Lung Transplant 1993;12(1 Pt 1):S14-8.
93. Wachtfogel YT, Kucich U, Hack CE, Gluszko P, Niewiarowski S, Colman RW, et al. Aprotinin inhibits the contact, neutrophil, and platelet activation systems during simulated extracorporeal perfusion. J Thorac Cardiovasc Surg 1993;106:1-10.
94. Daily PO, Lamphere JA, Dembitsky WP, Adamson RM, Dans NF. Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting. A randomized, prospective, double-blind study. J Thorac Cardiovasc Surg 1994;108:99-108.
95. Ovrum E, Am Holen E, Abdelnoor M, Oystese R, Ringdal ML. Tranexamic acid (Cyklokapron) is not necessary to reduce blood loss after coronary artery bypass operations. J Thorac Cardiovasc Surg 1993;105:78-83.
96. Arom KV, Emery RW. Decreased postoperative drainage with addition of epsilon-aminocaproic acid before cardiopulmonary bypass. Ann Thorac Surg 1994;57:1108-13.
97. Trinh-Duc P, Wintrebert P, Boulfroy D, Albat B, Thevenet A, Roquefeuil B. [Comparison of the effects of epsilon-aminocaproic acid and aprotinin on intra- and postoperative bleeding in heart surgery]. [French] Ann Chir 1992;46:677-83.
98. Nakashima A, Matsuzaki K, Fukumura F, Hisahara M, Kanegae Y, Fukae K, et al. Tranexamic acid reduces blood

loss after cardiopulmonary bypass. ASAIO J 1993;39:M185-9.

99. Karski JM, Teasdale SJ, Norman PH, Carroll JA, Weisel RD, Glynn MFX. Prevention of postbypass bleeding with tranexamic acid and epsilon-aminocaproic acid. J Cardiothorac Vasc Anesth 1993;7:431-5.
100. Blauhut B, Harringer W, Bettelheim P, Doran JE, Spath P, Lundsgaard-Hansen P. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994;108:1083-91.
101. DelRossi AJ, Cernaianu AC, Botros S, Lemole GM, Moore R. Prophylactic treatment of postperfusion bleeding using EACA. Chest 1989;96:27-30.
102. Goodnough LT, Price TH, Friedman KD, Johnston M, Ciavarella D, Khan N, et al. A phase III trial of recombinant human erythropoietin therapy in nonanemic orthopedic patients subjected to aggressive removal of blood for autologous use: dose, response, toxicity, and efficacy. Transfusion 1994;34:66-71.
103. Goodnough LT, Rudnick S, Price TH, Ballas SK, Collins ML, Crowley JP, et al. Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. N Engl J Med 1989;321:1163-8.
104. Watanabe Y, Fuse K, Naruse Y, Kobayashi T, Yamamoto S, Konishi H, et al. Subcutaneous use of erythropoietin in heart surgery. Ann Thorac Surg 1992;54:479-84.
105. Watanabe Y, Fuse K, Konishi T, Kobayasi T, Takazawa K, Konishi H, et al. Autologous blood transfusion with recombinant human erythropoietin in heart operations. Ann Thorac Surg 1991;51:767-72.
106. Neustein SM, Bronheim D, Galla J, Litwak R, Rand J, Scott BH, et al. Case 1—1993. The role of erythropoietin in Jehovah's Witnesses requiring cardiac surgery. J Cardiothorac Vasc Anesth 1993;7:95-102.
107. Salzman EW, Weinstein MJ, Weintraub RM, Ware JA, Thurer RL, Robertson L, et al. Treatment with desmopressin acetate to reduce blood loss after cardiac surgery. A double-blind randomized trial. N Engl J Med 1986;314:1402-6.
108. Hackmann T, Gascoyne RD, Naiman SC, Growe GH, Burchill LD, Jamieson WR, et al. A trial of desmopressin (1-desamino-8-D-arginine vasopressin) to reduce blood loss in uncomplicated cardiac surgery. N Engl J Med 1989;321:1437-43.
109. de Prost D, Barbier-Boehm G, Hazebroucq J, Ibrahim H, Bielsky MC, Hvass U, et al. Desmopressin has no beneficial effect on excessive postoperative bleeding or blood product requirements associated with cardiopulmonary bypass. Thromb Haemost 1992;68:106-10.
110. Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. A controlled clinical trial with thromboelastographic risk stratification. Anesthesiology 1992;77:38-46.
111. Brown MR, Swygert TH, Whitten CW, Hebeler R. Desmopressin acetate following cardiopulmonary bypass: evaluation of coagulation parameters. J Cardiothorac Anesth 1989;3:726-9.
112. Temeck BK, Bachenheimer LC, Katz NM, Coughlin SS, Wallace RB. Desmopressin acetate in cardiac surgery: a double-blind, randomized study. South Med J 1994;87:611-5.
113. Ansell J, Klassen V, Lew R, Ball S, Weinstein M, VanderSalm T, et al. Does desmopressin acetate prophylaxis reduce blood loss after valvular heart operations? A randomized, double-blind study. J Thorac Cardiovasc Surg 1992;104:117-23.
114. Reich DL, Hammerschlag BC, Rand JH, Weiss-Bloom L, Perucho H, Galla J, et al. Desmopressin acetate is a mild vasodilator that does not reduce blood loss in uncomplicated cardiac surgical procedures. J Cardiothorac Vasc Anesth 1991;5:142-5.
115. Blackstone EH, Kirklin JW, Stewart RW, Chenoweth DE. Damaging effects of cardiopulmonary bypass. In: Wu KK, Rossi EC, eds. Prostaglandins in clinical medicine: cardiovascular and thrombotic disorders. Chicago: Year Book Medical, 1982:355-69.
116. Downing SW, Edmunds LH Jr. Release of vasoactive substances during cardiopulmonary bypass. Ann Thorac Surg 1992;54:1236-43.
117. Butler J, Rocker GM, Westaby S. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 1993;55:552-9.
118. Boonstra PW, Gu YJ, Akkerman C, Haan J, Huyzen R, van Oeveren W. Heparin coating of an extracorporeal circuit partly improves hemostasis after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994;107:289-92.
119. Borowiec J, Thelin S, Bagge L, Hultman J, Hansson HE. Decreased blood loss after cardiopulmonary bypass using heparin-coated circuit and 50% reduction of heparin dose. Scand J Thorac Cardiovasc Surg 1992;26:177-85.
120. Jones DR, Hill RC, Hollingsed MJ, Stullken E, Graeber GM, Gustafson RA, et al. Use of heparin-coated cardiopulmonary bypass. Ann Thorac Surg 1993;56:566-8.
121. von Segesser LK, Garcia E, Turina MI. Low-dose heparin versus full-dose heparin with high-dose aprotinin during cardiopulmonary bypass. A preliminary report. Tex Heart Inst J 1993;20:28-32.
122. Ferraris VA, Berry WR, Klingman RR. Comparison of blood reinfusion techniques used during coronary artery bypass grafting. Ann Thorac Surg 1993;56:433-40.
123. Giordano GF, Rivers SL, Chung GKT, Mammana RB, Marco JD, Raczkowski AR, et al. Autologous platelet-rich plasma in cardiac surgery: effect on intraoperative and postoperative transfusion requirements. Ann Thorac Surg 1988;46:416-9.
124. Jones JW, McCoy TA, Rawitscher RE, Lindsley DA. Effects of intraoperative plasmapheresis on blood loss in cardiac surgery. Ann Thorac Surg 1990;49:585-90.
125. Tobe CE, Vocelka C, Sepulvada R, Gillis B, Nessly M, Verrier ED, et al. Infusion of autologous platelet rich plasma does not reduce blood loss and product use after coronary artery bypass. A prospective, randomized, blinded study. J Thorac Cardiovasc Surg 1993;105:1007-14.
126. Boey SK, Ong BC, Dhara SS. Preoperative plateletpheresis does not reduce blood loss during cardiac surgery. Can J Anaesth 1993;40:844-50.
127. Wong CA, Franklin ML, Wade LD. Coagulation tests, blood loss, and transfusion requirements in platelet-rich plasmapheresed versus nonpheresed cardiac surgery patients. Anesth Analg 1994;78:29-36.
128. Ereth MH, Oliver WC Jr, Beynen FMK, Mullany CJ, Orszulak TA, Santrach PJ, et al. Autologous platelet-rich plasma does not reduce transfusion of homologous blood products in patients undergoing repeat valvular surgery. Anesthesiology 1993;79:540-7,27A.
129. Mayer ED, Welsch M, Tanzeem A, Saggau W, Spath J, Hummels R, et al. Reduction of postoperative donor blood requirement by use of the cell separator. Scand J Thorac Cardiovasc Surg 1985;19:165-71.
130. Hall RI, Schweiger IM, Finlayson DC. The benefit of the Hemonetics cell saver apparatus during cardiac surgery. Can J Anaesth 1990;37:618-23.
131. Parrot D, Lancon JP, Merle JP, Rerolle A, Bernard A, Obadia JF, et al. Blood salvage in cardiac surgery. J Cardiothorac Vasc Anesth 1991;5:454-6.
132. Boldt J, Zickmann B, Czeke A, Herold C, Dapper F, Hempelmann G. Blood conservation techniques and platelet function in cardiac surgery. Anesthesiology 1991;75:426-32.

133. Boldt J, Kling D, von Bormann B, Zuge M, Scheld H, Hempelmann G. Blood conservation in cardiac operations. Cell separation versus hemofiltration. J Thorac Cardiovasc Surg 1989;97:832-40.
134. Nakamura Y, Masuda M, Toshima Y, Asou T, Oe M, Kinoshita K, et al. Comparative study of cell saver and ultrafiltration nontransfusion in cardiac surgery. Ann Thorac Surg 1990;49:973-8.
135. Sutton RG, Kratz JM, Spinale FG, Crawford FA Jr. Comparison of three blood-processing techniques during and after cardiopulmonary bypass. Ann Thorac Surg 1993;56:938-43.
136. Lonn U, Peterzen B, Granfeldt H, Casimir-Ahn H. Coronary artery operation with support of the Hemopump cardiac assist system. Ann Thorac Surg 1994;58:519-23.
137. Sellevold OF, Berg TM, Rein KA, Levang OW, Iversen OJ, Bergh K. Heparin-coated circuit during cardiopulmonary bypass. A clinical study using closed circuit, centrifugal pump and reduced heparinization. Acta Anaesthesiol Scand 1994;38:372-9.
138. Cosgrove DM, Amiot DM, Meserko JJ. An improved technique for autotransfusion of shed mediastinal blood. Ann Thorac Surg 1985;40:519-20.
139. Eng J, Kay PH, Murday AJ, Shreiti I, Harrison DP, Norfolk DR, et al. Postoperative autologous transfusion in cardiac surgery. A prospective, randomised study. Eur J Cardiothorac Surg 1990;4:595-600.
140. Morris JJ, Tan YS. Autotransfusion: is there a benefit in a current practice of aggressive blood conservation? Ann Thorac Surg 1994;58:502-8.
141. Page R, Russell GN, Fox MA, Fabri BM, Lewis I, Williets T. Hard-shell cardiotomy reservoir for reinfusion of shed mediastinal blood. Ann Thorac Surg 1989;48:514-7.
142. Roberts SR, Early GL, Brown B, Hannah H III, McDonald HL. Autotransfusion of unwashed mediastinal shed blood fails to decrease banked blood requirements in patients undergoing aortocoronary bypass surgery. Am J Surg 1991;162:477-80.
143. Shirvani R. An evaluation of clinical aspects of post-operative autotransfusion, either alone or in conjunction with pre-operative aspirin, in cardiac surgery. Br J Clin Pract 1991;45:105-8.
144. Schonberger JPAM, van Oeveren W, Bredee JJ, Everts PAM, de Haan J, Wildevuur CRH. Systemic blood activation during and after autotransfusion. Ann Thorac Surg 1994;57:1256-62.
145. Ward HB, Smith RRA, Landis KP, Nemzek TG, Dalmasso AP, Swaim WR. Prospective, randomized trial of autotransfusion after routine cardiac operations. Ann Thorac Surg 1993;56:137-41.
146. Axford TC, Dearani JA, Ragno G, MacGregor H, Patel MA, Valeri CR, et al. Safety and therapeutic effectiveness of reinfused shed blood after open heart surgery. Ann Thorac Surg 1994;57:615-22.
147. de Haan J, Schonberger J, Haan J, van Oeveren W, Eijgelaar A. Tissue-type plasminogen activator and fibrin monomers synergistically cause platelet dysfunction during retransfusion of shed blood after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1993;106:1017-23.
148. Bouboulis N, Kardara M, Kesteven PJ, Jayakrishnan AG. Autotransfusion after coronary artery bypass surgery: is there any benefit? J Card Surg 1994;9:314-21.
149. Tector AJ, Gabriel RP, Matericka WE, Oparah SS, Flemma RJ, Lepley D Jr. Reduction of blood usage in open heart surgery. Chest 1976;70:454-7.
150. Cohn LH, Fosberg AM, Anderson WP, Collins JJ Jr. The effects of phlebotomy, hemodilution and autologous transfusion on systemic oxygenation and whole blood utilization in open heart surgery. Chest 1975;68:283-7.
151. Ochsner JL, Mills NL, Leonard GL, Lawson N. Fresh autologous blood transfusions with extracorporeal circulation. Ann Surg 1973;177:811-7.
152. Petry AF, Jost T, Sievers H. Reduction of homologous blood requirements by blood-pooling at the onset of cardiopulmonary bypass. J Thorac Cardiovasc Surg 1994;107:1210-4.
153. Boldt J, Kling D, Weidler B, Zickmann B, Herold C, Dapper F, et al. Acute preoperative hemodilution in cardiac surgery: volume replacement with a hypertonic saline-hydroxyethyl starch solution. J Cardiothorac Vasc Anesth 1991;5:23-8.
154. Rao TKL, Montoya A. Cardiovascular, electrocardiographic and respiratory changes following acute anemia with volume replacement in patients with coronary artery disease. Anesthesiol Rev 1985;12:49-54.
155. Britton LW, Eastlund DT, Dziuban SW, Foster ED, McIlduff JB, Canavan TE, et al. Predonated autologous blood use in elective cardiac surgery. Ann Thorac Surg 1989;47:529-32.
156. Owings DV, Kruskall MS, Thurer RL, Donovan LM. Autologous blood donations prior to elective cardiac surgery. Safety and effect on subsequent blood use. JAMA 1989;262:1963-8.
157. Love TR, Hendren WG, O'Keefe DD, Daggett WM. Transfusion of predonated autologous blood in elective cardiac surgery. Ann Thorac Surg 1987;43:508-12.
158. Schmoeckel M, Nollert G, Mempel M, Mempel W, Reichart B. Effects of recombinant human erythropoietin on autologous blood donation before open heart surgery. Thorac Cardiovasc Surg 1993;41:364-8.
159. Toy PT, Strauss RG, Stehling LC, Sears R, Price TH, Rossi EC, et al. Predeposited autologous blood for elective surgery. A national multicenter study. N Engl J Med 1987;316:517-20.
160. Gravlee GP. Con: autologous blood collection is not useful for elective coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 1994;8:238-41.
161. Zipparo L, Gibson J. Study of the actual and potential utilization of autologous blood donation in four Central Sydney Area hospitals. J Qual Clin Pract 1994;14:65-75.
162. Van Dyck MJ, Baele PL, Leclercq P, Bertrand M, Brohet C. Autologous blood donation before myocardial revascularization: a Holter-electrocardiographic analysis. J Cardiothorac Vasc Anesth 1994;8:162-7.
163. Ferguson KJ, Strauss RG, Toy PT. Physician recommendation as the key factor in patients' decisions to participate in preoperative autologous blood donation programs: Preoperative Autologous Blood Donation Study Group. Am J Surg 1994;168:2-5.
164. Cordell AR, Lavender SW. An appraisal of blood salvage techniques in vascular and cardiac operations. Ann Thorac Surg 1981;31:421-5.
165. Keeling MM, Gray LA Jr, Brink MA, Hillerich VK, Bland KI. Intraoperative autotransfusion. Experience in 725 consecutive cases. Ann Surg 1983;197:536-41.
166. Giordano GF, Goldman DS, Mammana RB, Marco JD, Nestor JD, Raczkowski AR, et al. Intraoperative autotransfusion in cardiac operations. Effect on intraoperative and postoperative transfusion requirements. J Thorac Cardiovasc Surg 1988;96:382-6.
167. Millar AB, Armstrong L, van der Linden J, Moat N, Ekroth R, Westwick J, et al. Cytokine production and hemofiltration in children undergoing cardiopulmonary bypass. Ann Thorac Surg 1993;56:1499-1502.